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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/670,119	06/25/1996	GORDON Y.K. NG	SIM-001(7434	3008

21323 7590 08/13/2003

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EXAMINER
KAPUST, RACHEL B

ART UNIT	PAPER NUMBER
1647	31

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/670,119	NG ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,20-37 and 60-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,20-37 and 60-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

In Paper No. 20, claims 18, 20-37 and 60-65 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 18, 20-37 and 60-65 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. Claims 18, 20-22, 36, and 60-61 were rejected under 35 U.S.C. § 102(b) as being anticipated by Lofts *et al.* (1993), *Oncogene* 8: 2813-2820. Claims 18, 20-24, 29, 36-37, and 60-61 were rejected under 35 U.S.C. § 102(e) as anticipated by Murphy *et al.*, U.S. Patent No. 5,508,384.

Applicants filed an appeal to the Board of Patent Appeals and Interferences regarding the above-mentioned rejections. The Board found that the case was not in condition for a decision on appeal and vacated the pending rejections and remanded the application to the Examiner, in part for further consideration, and in part to more completely detail the considerations made on the record. Upon further review of the application and the opinion of the Board, PROSECUTION IS HEREBY REOPENED.

Claims 18, 20-37 and 60-65 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18, 20-37 and 60-65 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are directed to methods of treating, in a mammal, disorders for which administration of an antagonist of an integral membrane protein having at least one transmembrane domain is indicated. However, it is not clear whether the claims only embody the administration of the peptides as drugs or if they are also drawn toward the administration of an expression vector capable of expressing an effective amount of an antagonist peptide (*i.e.*, gene therapy). Applicants list on p. 16 of the specification that in one embodiment, "the invention provides new methods for gene therapy utilizing a genetically engineered, recombinant nucleotide sequence encoding a peptide antagonist, incorporated in a suitable transfection vector for introduction of the coding sequence into a selected cell or tissue." The language as recited in the claims can be interpreted to include said genetically engineered, recombinant nucleotide sequences encoding peptide antagonists.

So long as it does not introduce new matter, this rejection could be obviated by amending claim 18 such that it is drawn to an "isolated antagonist peptide" or an "antagonist peptide drug."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 20-26, 28-30, 32-33, 35-37, and 60-65 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for using the claimed peptide sequences that are antagonists to D1 or D2 dopamine receptors or β1- or α1A-adrenergic receptors, would still not reasonably provide enablement for effective analogues or fragments of said peptides or peptides of at least four amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention; 2) state of the prior art; 3) relative skill of those in the art; 4) level of predictability in the art; 5) existence of working examples; 6) breadth of claims; 7) amount of direction or guidance by the inventor; and 8) quantity of experimentation needed to make and/or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicants define an analogue as "any functional and/or chemical equivalent of a transmembrane amino acid sequence and includes peptides having one or more conservative amino acid substitutions, peptides incorporating unnatural amino acids and peptides having modified side chains" (p. 12, lines 18-25). Fragments may be selected by "truncation of one or more amino acids from the amino terminus of the transmembrane amino acid sequence, by truncation of one or more amino acids from the carboxy terminus or by truncation of one or more

amino acids from both amino and carboxy termini" (p. 7, line 33 through p. 8, line 3). Effective analogues or fragments are effective if they are a "functional equivalent of the transmembrane amino acid sequence" (p. 7, lines 20-24).

The only function assigned to the peptides of the invention is that they are specific antagonists of integral membrane proteins. The function, however, is neither novel nor unique to the peptides claimed. Marie *et al.* (1994, *J. Biol. Chem.* 269(33): 20815-20818, see p. 20815 column 1) teach that the pseudopeptidic ligand CGP 42112 A and the non-peptide ligand WL 19 specifically recognize the type 2 receptor (AT_2), a member of the G-protein coupled receptor superfamily. Shire *et al.* (1996, *J. Biol. Chem.* 271(12): 6941-6946, see p. 6941) teach that SR 141716A is a selective, potent antagonist of a cannabinoid receptor. Clearly, the function of being a specific antagonist to an integral membrane protein encompasses an infinite number of peptides and compounds.

In addition, of the peptides used in the working examples, all of the peptides were at least 14 amino acids in length. Most of the peptides were 20 amino acids in length. The specification fails to disclose any peptide that is 4 amino acids in length (referring to the "at least four amino acids" limitation in the claims) that acts as an antagonist to an integral membrane protein. Furthermore, the specification provides no guidance as to which (if any) of the transmembrane sequence amino acids can be changed or deleted to yield a functional equivalent of the transmembrane amino acid sequence. In their Brief, Applicants argued that "the present inventors have shown that antagonism of an integral membrane protein receptor is highly specific to transmembrane peptides of that receptor" (p. 10). Applicants have not, however, shown any examples of effective analogs or fragments of the antagonist peptides that are specific

to integral membrane protein receptors, and they have not provided any guidance for generating such analogs or fragments.

The amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted or deleted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie *et al.* (1990), *Science* 247: 1306-1310, especially p. 1306, column 2, paragraph 2; Wells (1990), *Biochemistry* 29: 8509-8517).

Since detailed information regarding the structural and functional requirements of the peptide antagonists is lacking, it is unpredictable as to which analogues and fragments, if any, meet the limitations of the claims. Therefore it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

Claims 18, 20-26, 28-30, 32-33, 35-37, and 60-65 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a genus, *i.e.* peptide antagonists of integral membrane proteins having at least one transmembrane domain. Applicants have disclosed certain peptides, SEQ ID NOS: 1-7 (D2 dopamine receptor peptides), 9-15 (D1 dopamine receptor peptides), 16-22 (β1-adrenergic receptor peptides), 23-29 (α1A-adrenergic receptor peptides), 30 (β1-adrenergic receptor peptide), 31 (α1A-adrenergic receptor peptide), and 55-61 (D2 dopamine receptor peptides), but have not disclosed sufficient species for the broad genus of any peptide or effective analogue of fragment thereof that is an antagonist to an integral membrane protein having at least one transmembrane domain.

The instant disclosure of specific peptides that are antagonists to dopamine and α1A- and β1-adrenergic receptors does not adequately describe the scope of the claimed genus, which encompasses hundreds of thousands of different peptides with varying structures and functions. For instance, Townsend-Nicholson *et al.* (1994, *J. Biol. Chem.* 269(4): 2373-2376) teach that mutation of the histidine residue in transmembrane domain VI of bovine α1A-adrenergic receptor results in a 3.8-fold decrease in antagonist affinity (p. 2373, column 2). The first point illustrated is that Townsend-Nicholson *et al.* have shown that making a single change within one transmembrane domain can have an effect on the receptor's affinity for an antagonist. Analogizing this to the current invention, while Applicants have disclosed specific peptides that can serve as antagonists to specific integral membrane proteins, they have not disclosed any

positions at which mutations may have either positive, deleterious, or no affect on the binding affinity for the integral membrane protein. They have not described the genus in a way such that one of skill in the art would be able to identify effective fragments and analogs of the antagonist peptides. Moreover, one of skill in the art would not think from the specification that Applicants had in their possession fragments or analogs of antagonist peptides.

The second point illustrated by Townsend-Nicholson *et al.* is that a mutation within one transmembrane domain can have an effect on the binding affinity for its antagonist. Applicants have disclosed antagonist peptides that are specific for the D2 dopamine receptor transmembrane domains VI and VII, the β1-adrenergic receptor transmembrane domain VII, and the α1A-adrenergic receptor domain VII. Members of the G protein-coupled receptor superfamily have seven transmembrane domains. Even more broadly, the claims are directed to integral membrane proteins having at least one transmembrane domain. There are hundreds and hundreds of integral membrane proteins. They are both structurally and functionally diverse. For example, proteins of the G protein-coupled receptor superfamily are known to function in many different physiological contexts: Vaughan (*J. Biol. Chem.* (1998), 273: 667-668) teaches that G proteins and the receptors with which they interact "influence virtually all kinds of cellular processes (p. 667). Hamm (*J. Biol. Chem.* (1998), 273: 669-672) teaches that "more than a thousand such receptors are known" (p. 669). Amongst all of the receptors that are encompassed by the claims, Applicants have only shown that specific transmembrane peptides may serve as antagonists to certain domains of certain receptors. Adequate written description requires more than a mere statement that something is part of the invention and reference to a potential method of using it. The compound itself is required.

Although sequences of some integral membrane proteins may be known in the art, it is not known whether a peptide antagonist having any transmembrane sequence (meaning domain 1, 2, 3, etc.) would be effective or if only certain transmembrane sequences for certain receptors would be effective. Moreover, it is not known whether sequences need to be specific as taught in the specification, or if analogues or fragments are effective. Thus, no identifying characteristics or properties of the instant peptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Therefore, only the methods for treating disorders for which administration of a specific antagonist (a peptide selected from the group consisting of SEQ ID NOS: 1-7, 9-31, and 55-61) of either D2 dopamine receptor, β1-adrenergic receptor, or an α1A-adrenergic receptor, but not the full breadth of the claim, meet the written description provision of 35 U.S.C. § 112, first paragraph.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18, 20-22, 36 and 60-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Lofts *et al.,* for the reasons made of record, and as follows.

Lofts *et al.* teach treatment of nude mice with an effective amount of a WT peptide sequence (see pg. 2814, Fig. 1), which comprises at least one transmembrane domain of the mammalian *neu*/EGF integral plasma membrane protein (*i.e.*, as it relates to a plurality of transmembrane domains in a tyrosine kinase receptor which extends intracellularly; as recited in claims 18, 20-22, 36 and 60-61), such that growth of solid tumors in these mice was reduced.

Lofts *et al.* specifically teach that the "small proteins all include a pentapeptide from position 661-665" and that such "sequences should interact with full-length receptors and prevent receptor dimerization and thus act as specific inhibitors of function" (*i.e.*, reasonably act as antagonists that consist essentially of at least four amino acid residues from at least one transmembrane domain, as claimed; see Abstract).

Applicants argue that Lofts *et al.* "did not conceive of using peptides consisting essentially of the amino acid sequence of the transmembrane domain only, or of fragments of that domain, nor did they conceive of administering any portion of an integral membrane protein as a drug" (Applicant's Brief, p. 8). As recited in the MPEP § 2111.03, "for the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355." As such, the peptides taught by Lofts *et al.* comprise an amino acid sequence of a transmembrane domain. If Applicants wish to have the claims interpreted more narrowly, the claims could be drawn to "peptides consisting of the transmembrane amino acid sequence."

In addition, as discussed above in the 112, second paragraph rejection, the claims as written encompass both peptide drugs and administration of an expression vector capable of expressing an effective amount of an antagonist peptide. Therefore, Lofts *et al.* anticipate the claims. This rejection could be obviated by distinguishing the claimed invention from methods encompassing gene therapy. For example, the claimed peptide could be an "isolated antagonist peptide" or an "antagonist peptide drug."

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. § 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. § 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

Claims 18, 20-24, 26, 28- 29, 36-37, and 60-61 are rejected under 35 U.S.C. § 102(e) as being anticipated by Murphy *et al.*, for the reasons made of record, and as follows.

Murphy *et al.* teach the use of isolated and/or recombinant G-protein coupled receptor (GPR) polypeptides which are fragments and/or sequences "having conservative amino acid substitutions, of at least one transmembrane domain of at least one G-protein coupled receptor" (column 6, lines 36-40). Said polypeptides may bind GPR ligands and they may also modulate, quantitatively or qualitatively, GPR ligand binding to GPRs. Regarding claims 24, 29, 60, and 61, the transmembrane domain may be from a GPR such as a dopamine receptor (column 7, lines 12-18), cAMP receptor, adenosine receptor, β-adrenergic receptor or α-adrenergic receptor (column 9, lines 38-65). The GPR polypeptides can include "GPR transmembrane domain fragments and/or consensus peptides thereof, of at leas[t] 4-10 amino acids in length, and/or corresponding sequences having conservative amino acid substitutions" (column 8, lines 37-44). In addition, Murphy *et al.* teach a method for treating a subject "suffering from a disease state

involving a qualitative or quantitative pathological abnormality of a GPR protein or a biological molecule functionally associated therewith" (column 7, lines 30-33).

Moreover, Murphy *et al.* teach the polypeptide sequence DDIFVTLDVLFSTASILNLSAISLKKK, the amino acid sequence of a GPR transmembrane polypeptide which corresponds to a portion of the dopamine D2 receptor transmembrane segment III (column 8, lines 3-6). Claims 26 and 28 are anticipated by the polypeptide of Murphy *et al.* as shown by the alignment with SEQ ID NO: 3 of the current invention (the exact matches are in bold):

IVF**TLDV**MMC**TASILNL**C**AISI** (SEQ ID NO: 3)
DD**I**FV**TLDV**LFS**TASILNL**S**AIS**LKKK (FIG. 2 OF US 5,508,384)

Even though the sequences are not 100% identical, the sequence taught by Murphy *et al.* is an effective analogue or fragment of SEQ ID NO: 3. More importantly, Murphy *et al.* claim a polypeptide having the amino acid sequence of SEQ ID NO: 2, thus the claim reads on Murphy *et al.*

Applicants argue that "one skilled in the art would not have appreciated the specificity of inhibition of the activity of an integral membrane protein achieved by administration of an antagonist peptide consisting essentially of at least four consecutive amino acid residues selected from the amino acid sequence of a transmembrane domain of that integral membrane protein" (p. 9 of Applicants' Brief). The issue is not whether one skilled in the art would have appreciated the specificity of inhibition achieved by the antagonist peptide, but whether said activity is an inherent property of the antagonist peptide. Murphy *et al.* teach peptides consisting essentially of at least four consecutive amino acid residues selected from the amino acid sequence of a

transmembrane domain. Murphy *et al.* teach using the peptides in both modulating G-protein coupled receptors (column 8, lines 63-66) and in methods for treating subjects suffering from a disease state involving a pathological abnormality of a GPR protein or a biological molecule functionally associated therewith (column 7, lines 29-33). Murphy *et al.* teach the peptides of claims 18, 20-24, 26, 28-29, 36-37, and 60-61. Murphy *et al.* teach "a method of treating, in a mammal, a disorder for which administration of an antagonist of an integral membrane protein having at least one transmembrane domain is indicated, said method comprising administering to the mammal an effective amount of an antagonist peptide consisting essentially of at least four consecutive amino acid residues from the amino acid sequence of said at least one transmembrane domain or a conservative amino acid substitution variant of said peptide to specifically inhibit the activity of the integral membrane protein" (claim 18). Because the specificity associated with the peptide is an inherent property, Murphy *et al.* anticipate the claims.

NO CLAIMS ARE ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (703) 305-0634. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 892-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RBK
August 11, 2003

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